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Real world data on Nexplanon® procedure-related events: final results from the Nexplanon Observational Risk Assessment study (NORA)☆,☆☆,★

Suzanne Reed [a,*], Thai Do Minh [a], Jens A. Lange [a], Carol Koro [b], Michelle Fox [b], Klaas Heinemann [a]

[a] Berlin Center for Epidemiology and Health Research (ZEG), 10115 Berlin, Germany
[b] Merck & Co., Inc., Kenilworth, New Jersey, US

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ABSTRACT

Objectives: We conducted this study to characterize the frequency of insertion-, localization- and removal-related events and their clinically significant consequences among Nexplanon® (etonogestrel radiopaque contraceptive implant) users in the United States during standard clinical practice.
Study design: The Nexplanon Observational Risk Assessment (NORA) study was a large, prospective cohort study conducted in the United States. A total of 428 Health Care Professionals (HCPs) who had completed the Nexplanon clinical training program recruited women who were newly prescribed Nexplanon. We collected data on insertion-, localization- and removal-related events experienced during routine clinical practice via questionnaires completed by patients and HCPs. Recruitment began in December 2011 and follow-up ended in October 2017. Data analysis characterized the frequency of procedure-related events.
Results: We collected data on 7364 insertion procedures. The incidence of incorrect insertion (i.e., initially unrecognized non-insertion, partial insertion or deep insertion) was 12.6 per 1000 insertions (95% CI, 10.2–15.5). Pins and needles/numbness in the arm/hand/fingers was the most common patient-reported event. We obtained data on 5159 removal procedures, of which all were successful but one (due to the location of the implant in deep muscle tissue). No implants were localized outside the arm. The most common challenge reported by HCPs during implant removal was encasement of the implant within fibrotic tissue.
Conclusions: Events associated with the insertion, localization and removal of the Nexplanon contraceptive implant were rare and their clinical consequences were generally not suggestive of serious injury.
Implications: This study is the largest prospective evaluation of events associated with insertion and removal of Nexplanon during routine clinical practice. It demonstrates that complications associated with insertion and removal of Nexplanon are rare when performed by trained clinicians.

1. Introduction

Nexplanon®, also known as Implanon-NXT® outside the United States (US), is a subdermal etonogestrel radiopaque implant that provides contraception for 3 years. It differs from the originally marketed etonogestrel implant (Implanon®) by the addition of barium sulfate and a new applicator design. These changes were developed to aid implant localization by making it radiopaque [i.e., visible via X-ray and Computerized Tomography (CT)] and to facilitate single-handed correct insertion.

Incorrect (i.e., too deep or at the wrong location) implant insertion may result in symptoms of neurovascular injury if the implant is placed on or near a nerve, including the ulnar nerve which runs superficially near the elbow [1–3]. Implants inserted too deeply may cause neurovascular injury at the time of insertion or removal [4]. In very

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* Corresponding author: Tel.: +49 171 264 5691.
E-mail address: reed@zeg-berlin.de (S. Reed).

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rare cases, intravascular insertion may cause migration of the implant to the pulmonary artery [5]. However, data on the incidence of insertion- and removal-related events or their associated risk factors are sparse. In this large post-approval study mandated by the US Food and Drug Administration (FDA), we measured the occurrence of insertion- and removal-related events and evaluated factors which may impact upon these events, such as BMI, repeat/consecutive use and health care professional (HCP) experience.

2. Materials and methods

The primary objective of the Nexplanon Observational Risk Assessment (NORA) study was to characterize the frequency of specific insertion-, localization- and removal-related events and clinically significant consequences thereof among Nexplanon users in the US during standard clinical practice. These events included: incorrect insertion (including unrecognized non-insertion, partial insertion and deep insertion), non-palpability of the implant at insertion and removal, localization of non-palpable implants, and difficult removals. Clinically significant consequences included: pregnancy due to unrecognized non-insertion, nerve or vascular injury, and hospitalization and/or surgery for localization and/or removal.

In this large, prospective, cohort study, women were invited by their HCPs to participate after they had received a prescription for a Nexplanon implant. The women were then followed from the day of Nexplanon insertion until 6 months after removal. These included first-time users and repeat/consecutive users of any implant. Repeat users had a contraceptive implant previously that was not present at the time of enrollment. Consecutive users had another contraceptive implant removed immediately preceding insertion of the study implant. We obtained ethical approval from the Western Institutional Review Board (WIRB) and an independent Safety Monitoring and Advisory Council monitored the study.

2.1. Study population

Health Care Professionals who completed training sponsored by the marketing authorization holder for Nexplanon (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) were invited to participate. This training, which involves lectures, videos and hands-on simulation, is required of all HCPs who order and insert Nexplanon within the US. HCPs recruited patients during routine practice; we do not have data on patients who declined participation. We planned a sample size of 7100 to detect events occurring in 1 per 1000 insertions. All women prescribed a new implant by participating HCPs could participate if they understood their role in the study, completed the self-administered questionnaire (in English) and signed consent.

2.2. Baseline survey and follow-up

HCPs and their patients completed a baseline questionnaire immediately after insertion. HCPs provided information on the insertion procedure, including the palpability of the implant, methods used to localize non-palpable implants, the location of the implant and challenges encountered during insertion. Patients reported their age, weight, height, previous contraceptive use, medical history and significant events in the arm in which the implant was just inserted. We then followed up participants every 6 months and collected the final follow-up questionnaire 6 months after implant removal (regardless of when it was removed) or 42 months after insertion if the implant was still in situ at 36 months. We used follow-up participant questionnaires to gather information on significant and/or serious adverse events (including pregnancies and symptoms related to possible neurovascular injury), general health, and localization and/or removal procedures. We asked HCPs performing removal or localization procedures to complete questionnaires to record complications, implant location and palpability, methods used to localize non-palpable implants, patient hospitalization and the outcome of the removal procedure.

We conducted a four-level follow-up process to minimize loss of information. Level 1 activities included mailing the questionnaire and, if there was no response, two reminders. Level 2 activities included multiple telephone attempts to participants and their listed contacts. Thereafter, we searched telephone and address directories (Level 3). If these efforts were unsuccessful, we contacted the HCP who inserted the implant to ascertain whether the implant had been removed and, if applicable, to collect a Localization/Removal Questionnaire (Level 4).

2.3. Data analysis

We produced descriptive statistics to summarize baseline characteristics and calculated point-estimates of event rates and their 95% CIs. We analyzed the impact of potential prognostic factors with multivariate regression models and/or stratified analyses. We categorized HCP experience as <5 Nexplanon insertions or ≥5 Nexplanon insertions at the time of a patient's insertion procedure. For outcomes of interest, we calculated absolute numbers and incidence proportions (number of events per 1000 insertions) with 95% CIs according to Clopper & Pearson [6]. When appropriate, we determined incidence proportions per 1000 follow-up questionnaires or removal procedures. We performed all statistical analyses using SAS 9.3.

3. Results

3.1. Study participants

A total of 428 HCPs in 47 states recruited 7364 patients between December 2011 and March 2014. The recruitment target of 7100 patients was inadvertently exceeded when, toward the end of recruitment, HCPs returned in bulk the baseline study documents of recruited patients. Gynecologists (n=3360; 45.6%), nurse practitioners (n=3351; 45.5%), general practitioners (n=336; 4.6%), physician assistants (n=300; 4.1%) and nurses (n=17; 0.2%) performed the insertions. Follow-up ended in October 2017.

Analyses are based on Nexplanon insertions in 7364 women; we excluded 14 women because the baseline questionnaire pre-dated signed consent, and we excluded 6 others due to language barriers. Participants included 6468 first-time users and 896 repeat/consecutive users (87.8% and 12.2% of participants, respectively). Descriptive statistics are presented in Table 1.

3.2. Loss to follow-up

We obtained removal information on 5159 participants (70.1%). Others discontinued participation in the study (897 participants; 12.2%), had the implant in place at the end of the study (having used it longer than 36 months) (390 participants; 5.3%), or were lost to follow-up (918 participants; 12.5%). Fig. 1 contains a flow diagram showing the progress of the patients through the study.

Table 1
Baseline characteristics of Nexplanon users by user status (first-time versus repeat/consecutive users*)

	First-time users	Repeat/Consecutive users	All users
No. of users (%)	6468 (87.8)	896 (12.2)	7364 (100.0)
Mean age (SD)	22.9 (5.7)	25.5 (6.6)	23.2 (5.9)
Mean BMI (SD)	27.8 (7.0)	29.6 (8.2)	28.0 (7.2)

* Repeat users had previously used a contraceptive implant but not immediately preceding enrollment. Consecutive users had another contraceptive implant removed immediately preceding insertion of the study implant.

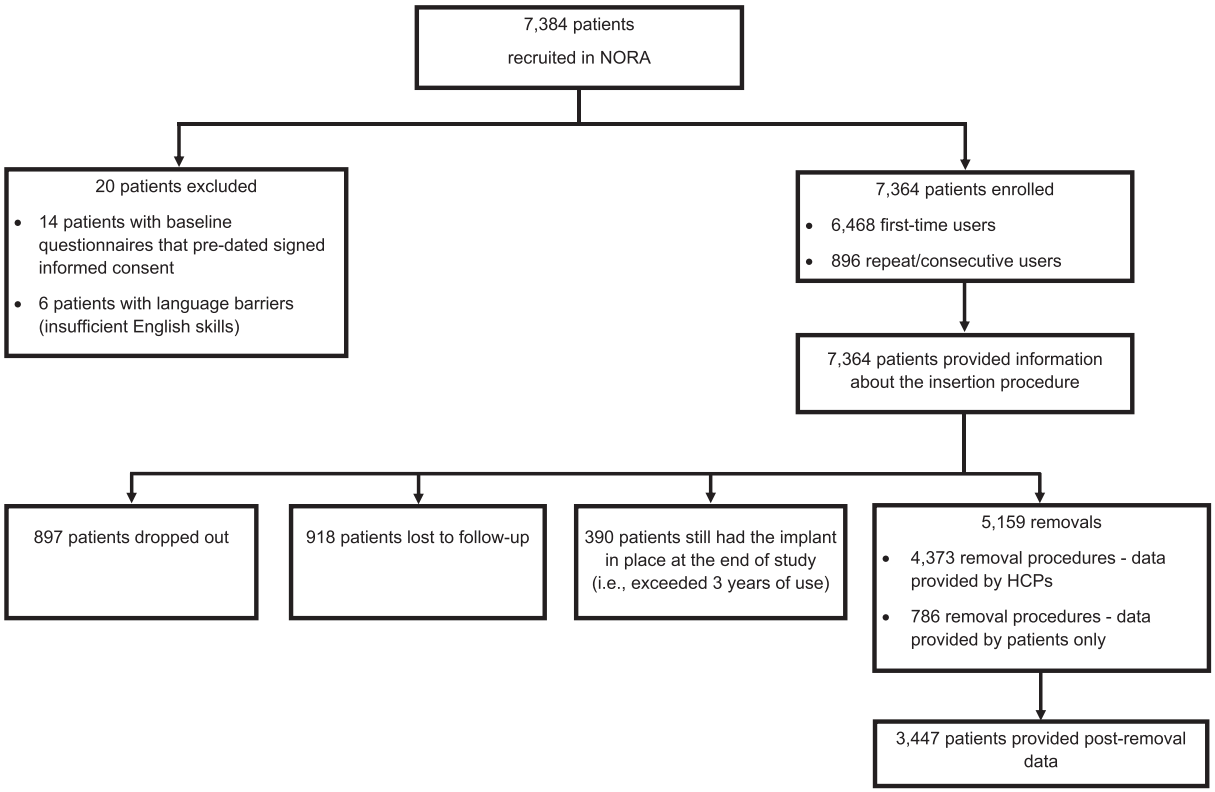

Fig. 1. Flow diagram showing the progress of patients through the NORA study.

3.3. Clinician-reported events at insertion

Following 7364 insertions, 85 HCPs reported 208 insertion-related events involving 189 patients. There were 93 incorrect insertions (12.6 per 1000 insertions; 95% CI, 10.2–15.5) which included 65 deep insertions (8.8 per 1000 insertions; 95% CI, 6.8–11.2), 27 partial insertions (3.7 per 1000 insertions; 95% CI, 2.4–5.3) and 1 (initially) unrecognized non-insertion (0.1 per 1000 insertions; 95% CI, 0.0–0.8). There were no significant differences according to HCP prior experience with Nexplanon insertion (i.e., fewer than 5 insertions at the time of a patient's insertion versus at least 5 insertions). Incorrect insertion included unrecognized non-insertion (i.e., implant thought to have been placed but months later confirmed to be absent by undetectable serum etonogestrel), partial insertion (i.e., implant protruding from the skin) and deep insertion. In this study, we defined deep insertion to include non-palpable implants following insertion, implants within muscle or adjacent to the deep fascia overlying the muscle, and injury to a nerve or blood vessel during insertion.

We classified 65 insertions as deep (8.8 per 1000 insertions; 95% CI, 6.8–11.2). We stratified by age group, BMI category and user status (i.e., first-time vs. repeat/consecutive user) but saw no significant differences in the proportion of deep insertions between groups. One hematoma developed along the needle track immediately after insertion. Although the implant was palpable in this case, we considered the event a 'deep insertion' due to vascular injury. Two deeply inserted implants were located within muscle and 56 were reported adjacent to the deep fascia. A further 6 deeply inserted implants were not palpable but not reported to be located within muscle or adjacent to the deep fascia; 3 were localized via X-ray and left in situ, in one case no further action was taken to localize the implant (it was removed successfully several months later) and in 2 other cases the HCP did not specify whether additional efforts were made to localize the implants (1 of these implants was removed 3 years later and in the other case, it is unknown whether the implant was removed).

One HCP reported 26 deep insertions; the HCP reported this complication in over 60% of implants placed. These implants were palpable but described as adjacent to the deep fascia (and we therefore classified them as

Table 2
Insertion-related challenges reported by HCPs immediately after the Nexplanon insertion procedure: Numbers and incidence proportions per 1000 insertions (and 95% CIs)

	No. Insertions (N=7364)	Incidence proportion per 1000 insertions	95% CI
Difficulty removing the protection cap	93	12.6	10.2–15.4
Difficulty sliding the needle to its full length into the skin	30	4.1	2.8–5.8
Needle stick injury (to the HCP)	1	0.1	0.0–0.8
Difficulty unlocking the purple slider	6	0.8	0.3–1.8
Needle inserted too deep	2	0.3	0.0–1.0
Difficulty moving purple slider fully to the back	14	1.9	1.0–3.2
Needle inserted too superficially	1	0.1	0.0–0.8
Needle visible after insertion (not fully retracted)	4	0.5	0.1–1.4
Other	29	3.9	2.6–5.7
Difficulty handling the device/visualization	17	2.3	1.4–3.7
Reaction at the insertion site	5	0.7	0.2–1.6
Difficulty penetrating the skin with the needle	3	0.4	0.1–1.2
Patient reaction to insertion procedure	4	0.5	0.2–1.4

Table 3
Events reported by patients immediately after the Nexplanon insertion procedure: Numbers of events in the arm in which the implant was inserted and incidence proportions per 1000 insertions (and 95% CIs) by user status

	First-time users (*N*=6468)			Repeat/consecutive users (*N*=896)			All users (*N*=7364)		
	n	IP[a]	95% CI	n	IP[a]	95% CI	n	IP[a]	95% CI
Any event[b]	30	4.6	3.1–6.6	19	21.2	12.8–32.9	49	6.7	4.9–8.8
Pins and needles/numbness	8	1.2	0.5–2.4	9	10.0	4.6–19.0	17	2.3	1.4–3.7
Severe pain	6	0.9	0.3–2.0	4	4.5	1.2–11.4	10	1.4	0.7–2.5
Altered strength/movement	2	0.3	0.0–1.1	1	1.1	0.0–6.2	3	0.4	0.1–1.2
Injury to blood vessels or blood clots in arm	1	0.2	0.0–0.9	1	1.1	0.0–6.2	2	0.3	0.0–1.0
Other	17	2.6	1.5–4.2	5	5.6	1.8–13.0	22	3.0	1.9–4.5

[a] Incidence proportion per 1000 insertions.
[b] Limited to one event per woman.

'deep'). All of these "deeply placed" implants with follow-up information (*n*=24) were palpable at removal and were successfully removed. Excluding those 26 cases, the rate of deep insertion was 6.0 per 1000 insertions (95% CI, 4.3–8.0). We identified no significant differences in the proportion of incorrect insertion between physicians and non-physicians.

Other insertion challenges involved handling the Nexplanon device (e.g. difficulty removing the protection cap) as shown in Table 2.

3.3.1. Patient-reported events at insertion

Immediately following insertion, 49 patients reported 54 events in the arm containing the implant (Table 3). Some reported multiple events that were potentially related (e.g., altered strength which could result from severe pain). Patients most commonly reported pins/needles/numbness in the arm/hand/fingers (2.3 per 1000 insertions; 95% CI, 1.4–3.7) and this event was statistically significantly more likely among repeat/consecutive users (10.0 per 1000 insertions; 95% CI, 4.6–19.0) than first-time users (1.2 per 1000 insertions; 95% CI, 0.5–2.4). We stratified by age group and BMI category but identified no statistically significant differences in the proportions of types of events or 'any event'. Patients whose implant was inserted by a less experienced HCP (i.e., <5 insertions) were significantly more likely to report severe pain (6.1 per 1000 insertions; 95% CI, 2.3–13.3) after insertion than those whose implants were placed by more experienced clinicians (0.6 per 1000 insertions; 95% CI, 0.2–1.6).

3.3.2. Patient-reported events during follow-up

A total of 369 patients reported 646 significant events in the arm containing the implant during follow-up (Table 4). To confer an objective measure of 'significant event', we restricted the analysis to events for which the patient reported having visited a physician. During follow-up, patients most commonly reported pins/needles/numbness in the arm/hand/fingers (23.8 per 1000 insertions; 95% CI, 20.4–27.5), but the statistically significant difference between first-time and repeat/consecutive users observed immediately after insertion was no longer present. First-time users were more likely to report severe pain in the implant arm (25.4 per 1000 insertions; 95% CI, 21.7–29.5) during follow-up than repeat/consecutive users (12.3 per 1000 insertions; 95% CI, 6.1–21.9). Stratifying by age group and BMI category revealed no significant differences in the incidence of events.

3.4. Nexplanon localization/removal procedures

Overall, we obtained information on 5159 removals. HCPs provided details of 4373 of the 5159 removals and data on an additional 786 removals were obtained only from the patients (when the relevant HCP could not be located or did not respond to our requests for information). All reported attempted removals were successful except one. Two of the successful removals were performed by the patient herself (reportedly due to financial/insurance reasons). In the one unsuccessful removal attempt, the HCP reported that the implant was palpable but located within deep muscle and could not be removed using local anesthesia in the clinic; it is unknown if the implant was subsequently removed because the patient reached the end of the follow-up phase with the implant still in place.

In addition to providing information on 4373 removals, HCPs also provided data on 46 procedures involving only the localization of an implant (without an attempt to remove it). Therefore, in total, we obtained data on 4419 localization and/or removal procedures involving 4390 patients (in some cases, HCPs returned more than one survey per patient; for example, if an HCP localized an implant but left in situ and then removed the implant during a subsequent visit). HCPs reported no neurovascular injuries. During the 4419 localization and/or removal procedures, 18 implants (0.4% of patients with HCP reports) were not palpable. Of these 18 non-palpable implants, 11 were localized and removed, one was localized and left in situ, and 6 were not localized and not removed at last follow-up. In the latter six cases, the following modalities were used but were unsuccessful and no removal procedure

Table 4
Events reported by patients at any time during the follow-up phase while using Nexplanon: Numbers of events in the arm in which Nexplanon was inserted and incidence proportions per 1000 insertions (and 95% CIs) by user status

	First-time users (*N*=6468)			Repeat/consecutive users (*N*=896)			All users (*N*=7364)		
	n	IP[a]	95% CI	*n*	IP[a]	95% CI	*n*	IP[a]	95% CI
Any event[b]	338	52.3	47.0–58.0	31	34.6	23.6–48.8	369	50.1	45.2–55.3
Pins and needles/numbness	185	28.6	24.7–33.0	19	21.2	12.8–32.9	204	27.7	24.1–31.7
Severe pain	164	25.4	21.7–29.5	11	12.3	6.1–21.9	175	23.8	20.4–27.5
Altered strength/movement	70	10.8	8.5–13.7	6	6.7	2.5–14.5	76	10.3	8.1–12.9
Other	95	14.7	11.9–17.9	10	11.2	5.4–20.4	105	14.3	11.7–17.2

[a] Incidence proportion per 1000 insertions.
[b] Limited to one event per woman. Some patients reported different arm-related events (for which they visited a physician) at different time points. This analysis did not differentiate between specific types of arm-related events and it was therefore not necessary to decide which event was taken into consideration (i.e. it counted as an event – any event – for which the patient visited a physician).

Table 5
Challenges encountered by HCPs during the Nexplanon removal procedure: Numbers and incidence proportions per 1000 removal procedures (and 95% CIs) by user status

	First-time users (*N*=3881)			Repeat/consecutive users (*N*=492)			All users (*N*=4373)		
	n	IP[a]	95% CI	*n*	IP[a]	95% CI	*n*	IP[a]	95% CI
Any event[b]	49	12.6	9.4–16.7	11	22.3	11.2–39.6	60	13.7	10.5–17.6
Encased in fibrotic tissue	22	5.7	3.6–8.6	7	14.2	5.7–29.0	29	6.6	4.4–9.5
Multiple attempts required	12	3.1	1.6–5.4	1	2.0	0.1–11.3	13	3.0	1.6–5.1
Implant too deep	7	1.8	0.7–3.7	4	8.1	2.2–20.6	11	2.5	1.3–4.5
Implant migrated	4	1.0	0.3–2.6	2	4.1	0.5–14.6	6	1.4	0.5–3.0
Other	12	3.1	1.6–5.4	2	4.1	0.5–14.6	14	3.2	1.8–5.4

[a] Incidence proportion per 1000 removals.
[b] Limited to one event per removal procedure.

was initiated: ultrasound (three cases), unspecified methods (two cases) and ultrasound plus X-ray (one case). In one of these cases involving a non-localized implant, the patient presented approximately 7 months pregnant 30 months after insertion. Etonogestrel was not detected by serum assay, indicating no implant was present; this case was considered a previously unrecognized non-insertion (although an unrecognized implant expulsion cannot be excluded). Etonogestrel was not tested in the other cases.

3.4.1. Removal-related events reported by HCPs

As shown in Table 5, HCPs reported 73 challenging events during 60 removals (13.7 per 1000; 95% CI, 10.5–17.6). HCPs most commonly reported encasement within fibrotic tissue (6.6 per 1000; 95% CI, 4.4–9.5). HCPs reported this more than twice as often in the repeat/consecutive user group (14.2 per 1000; 95% CI, 5.7–29.0) than the first-time user group (5.7 per 1000; 95% CI, 3.6–8.6), although the difference was not statistically significant. In 11 cases, the HCP reported challenges due to a deeply located implant (2.3 per 1000; 95% CI, 1.5–4.5); 8 of these implants were palpable, 2 were not palpable and in 1 case palpability was not specified. One of these deep implants could not be removed in the clinic (this was the unsuccessful removal attempt described in Section 3.4).

Five implants were removed successfully within a hospital (4 deeply inserted implants and one in the setting of an infection). In one of these cases involving removal of a deeply placed implant under general anesthesia, the patient experienced moderate post-operative pain along the pathway of the ulnar nerve.

HCPs reported local implant migration in 48 cases (1.1% of the 4390 procedures reported); however, only 6 cases of local migration caused difficulty during removal. No implants which were localized were positioned outside the arm; no intravascular insertions were reported.

Stratified analyses showed no statistically significant effect of age, BMI or user status (first-ever vs. repeat/consecutive) on localization- and removal-related events.

3.4.2. Clinically significant consequences of removal-related events

Six months or more following implant removal, we collected post-removal data on 3447 women (47% of participants), of which 42 (12.2 per 1000 questionnaires received; 95% CI, 8.8–16.4) reported visiting a physician for events localized to the arm from which the implant had been removed. Pins/needles/numbness in the arm/hand/fingers was most common, with an incidence of 7.0 per 1000 post-removal questionnaires (95% CI, 4.5–10.3), followed by severe pain (3.2 per 1000 questionnaires; 95% CI, 1.6–5.7) and altered strength/movement (2.3 per 1000 questionnaires: 95% CI, 1.0–4.6).

4. Discussion

Clinically significant events associated with insertion, localization, and removal of Nexplanon were rare and generally not suggestive of serious injury. Except for one report of post-operative pain along the ulnar nerve pathway following removal of a deeply inserted implant, there were no reports of nerve injury. Other than a hematoma along the insertion track, no vascular complications were reported.

The higher rates of paresthesia reported in repeat/consecutive users immediately following insertion could be due to simultaneous removal and insertion of an implant which requires more tissue manipulation and anesthetic than insertion alone. This may result in increased irritation at the insertion site.

The ability to localize an implant is dependent upon the types of imaging procedures performed. These procedures were limited to ultrasound for three of the six non-palpable implants not localized and not removed at time of last follow up. However, Nexplanon may be localized by X-ray, CT, and magnetic resonance imaging; use of these imaging modalities may have been successful.

A previous study reported migration of the implant of up to 2 cm (cm) in 54% of implants at 1 year (n=87) with only 1% migrating beyond 2 cm [7]. No implants in this study were localized beyond the arm and none were localized in an intravascular location within the arm.

Strengths of the study include a low lost-to-follow rate (12.5%) and collection of data from two sources (the patients and their HCPs). We collected removal data on 70% of participants, which allowed a reliable assessment of the risk of events that occur at a rate of 1 in 1000 insertions/removals.

There are inherent limitations in observational research, including the inability to completely exclude the effects of bias [8]. However, selection bias was unlikely to have had a substantial impact for the following reasons: participating HCPs included physicians and non-physicians widely distributed across the US, all trained and with varying prior experience with contraceptive implants. The HCPs were expected to enroll all eligible patients in whom they placed an implant, thereby minimizing enrollment bias. However, information on patients declining participation was not collected.

The rates of HCP-reported events may have been overestimated due to preferential reporting by some HCPs; one HCP reported that over 60% of implants inserted were “adjacent to the fascia” and thus categorized as “deep” despite being palpable.

Despite its large size, this study was not powered to detect events that occur at less than 1 in 1000. Clinicians and patients should be aware that published case reports demonstrate the potential for neurovascular injury [1–3] and pulmonary artery migration of contraceptive implants [5]; however, these events are extremely rare.

Only events in the implant arm for which the patient reported visiting a clinician were included in the follow-up analyses. It is possible events occurred in those lost to follow-up or in women who lacked resources (financial or otherwise) to seek care. Inclusion of all patient-reported symptoms in the analyses would increase the rates of insertion- and removal-related events.

Despite the limitations of observational research, this study benefited from methodology that optimized the validity and generalizability of its findings. It demonstrates the safe use of single rod etonogestrel implants placed by a variety of HCPs.

To our knowledge, this study is the largest cohort involving Nexplanon and it shows that clinically significant complications associated with insertion and removal are rare.

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